Breast cancer and pregnancy: a review

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Introduction

Breast cancer afflicts one in 12 women in the UK causing 14 000 deaths per annum. In up to 3% of these cases there is an association with pregnancy[1] which may be coincident breast cancer during pregnancy or lactation, or development of the cancer up to one year postpartum. This makes it the second commonest malignancy seen during pregnancy (cervical being commonest) - occurring in between 10 and 39 per 100 000 pregnancies.

Currently about 15% of breast cancers are seen in women of child-bearing age, and the current trend in many populations to delay pregnancy until a later age may increase this proportion. There is also considerable evidence that the incidence of breast cancer in premenopausal women is increasing[2].

Popular myths

A clinician's experience of gestational breast cancer is usually limited to a handful of individual cases, and the management strategy is often rooted in obsolete teachings and philosophies. We carried out an informal survey of consultant general surgeon, obstetrician and principal general practitioner colleagues, asking whether they had any personal experience of pregnancy-associated breast cancer, and if so how they would manage it. Of the 15 colleagues polled, all answered, but the correlation between answers was negligible (see Figure 1).

None of the general practitioners asked had been involved in the treatment of this condition, but all general surgeons and obstetricians had treated either patients with concurrent breast cancer and pregnancy or women who had suffered breast cancer and subsequently become pregnant. All GPs and surgeons thought that pregnancy confers a worse prognosis - reasons given include an excess of inflammatory breast carcinoma, the hormonal changes of pregnancy causing increased tumour growth, inherent aggressiveness of these tumours or the relative youth of the patients. None thought that diagnostic delay contributed to the poor prognosis of these patients. Obstetricians did not believe these patients did worse. Views concerning therapeutic abortion varied, although none thought that this should be mandatory; most thought that either it was unnecessary or only needed if adjuvant therapy was contemplated, or in the first trimester. The respondents were asked if they thought subsequent pregnancy may promote recurrence - most GPs admitted they did not know, most surgeons thought that it may, and obstetricians views were diverse. The effect of chemotherapy on fertility was thought to be negligible by GPs, whilst surgeons and obstetricians thought it may sometimes cause sterility. When asked what advice they would give to a patient on subsequent conception most clinicians felt the patient should wait 2 years, although 50% of GPs did not know. A frequent comment by GPs was that they would seek specialist advice from a general surgeon or obstetrician in this situation. Yet it appears that 'specialist advice' has not reached a consensus.

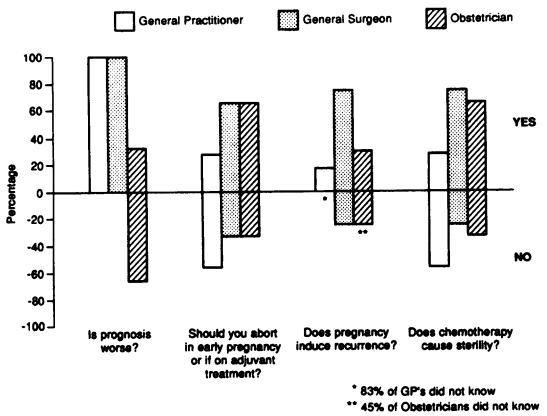

Figure 1. Results of a survey into how various doctors would manage gestational breast cancer

Thus the idea that gestational breast cancer is somehow a different disease to that seen in non-pregnant women appears widespread. It was first noted by Samuel Gross in 1880 'its growth was wonderfully rapid and its course excessively malignant'. This belief led to a zealous enthusiasm for aborting the pregnancies of these patients, and even to Haagenson declaring in 1943[3] that no patient with breast cancer diagnosed during pregnancy should undergo surgery because they were incurable. This attitude has gradually abated, and it has been shown that the outcome in patients with concurrent breast cancer and pregnancy is the same, when matched for age and stage of disease, as their non-pregnant counterparts[4,5]. Equally it appears that subsequent pregnancies after treatment for breast cancer may actually improve the patients chance of long term survival[6].

The belief that breast cancer in premenopausal women is more likely in pregnancy than at any other time is not borne out by the data available. Women aged 25-40 years have 180 months of 'at risk' time, and on average are pregnant for 18 of these, ie 10%. Breast tumours occurring in pregnancy are found in 11% of this age group of women - a figure which concurs almost exactly with chance.

Yet a woman diagnosed with breast cancer during pregnancy or lactation is more likely to fare worse than a woman of a similar age who is not pregnant. If this is not due to a difference in disease behaviour then it must be due to a later stage of disease at presentation. Why should this be so?

Diagnostic delay

Various studies show that 56-89% of patients who present with breast cancer in pregnancy are lymph node (LN) positive[7]. This high prevalence of advanced disease implies that either the disease in pregnant women is more aggressive or that there is a delay in diagnosis. Analysis of age and stage matched pregnant and non-pregnant groups shows an identical 5 year survival. Thus the disease does not appear to be more aggressive in pregnant women and by implication there is a diagnostic delay. This is borne out in a number of series[8-13]; the delay being anything from an average of 2 months[8] to 15 months[6] more than non-pregnant women. At first sight this appears contradictory to expectations - after all a pregnant woman usually undergoes a full physical examination including a breast examination by a doctor at least once during her pregnancy. However the physiological hypertrophy often masks a lump, or any abnormality detected may be attributed to the normal breast changes of pregnancy. Mammography is rarely performed because of the perceived potential harm to the fetus, and even if it is, is rarely useful because of an increase in breast density.

Most breast abnormalities presenting during the gestational period are benign, the differential diagnosis including cysts, fibroadenomas, lipomas, galactocoeles, localized infarcts and inflammatory conditions. However a carcinoma must always be suspected, and histology requested on all surgical specimens, including the abscess wall. Coincident pathology such as lobular hyperplasia or lactational mastitis has been reported in up to 30% of breast cancers diagnosed during a pregnancy[9].

Pathology and biology

The pathology is identical to that found in non-pregnant women, including the incidence of inflammatory carcinoma of 1.5-4%[14]. In common with other pre-menopausal patients, most of these cancers are oestrogen receptor (ER) and progesterone receptor (PR) negative[13,15]. Assay of ER status may give an excess of false negatives in these patients due to high levels of circulating oestrogens saturating all available ER sites. Clinical evidence of ER negativity comes from lack of objective response of these patients to oophrectomy[16]. There are, of couse, many other hormonal changes occurring in the pregnant woman, including changes in corticosteroids, growth hormone, insulin and prolactin. The effects of these on tumour growth is unknown. Although it is well documented that prolactin promotes murine mammary tumour growth[17], its effects in human breast cancer are less clear[18]. The altered immunocompetence seen in pregnancy, with a fall in T-cells[19] and a decreased activity of lymphocytes against mitogens[20] has also been suggested as a factor in tumour spread. More work is awaited.

Remaining alert to the possibility of breast cancer and careful breast examination in early pregnancy is vital if we are to improve on our poor record of prompt detection of this disease.

Treatment

The treatment of breast cancer in pregnant women should adhere to the same criteria as their non-pregnant counterparts, and there is no justification for delay in treatment[21]. Fine needle aspiration cytology or biopsy may be safely performed on suspicious lumps to confirm the diagnosis.

Staging procedures on the whole are not detrimental to the fetus - the only possible exception being a bone scan, although even this is thought to be acceptable if the patient is kept well hydrated and catheterized so there is no delay in excretion of the Tc-99 methylene diphosphonate. However, little is lost in avoiding staging procedures for clinically Stage I and II disease where the return is so small.

Termination of pregnancy is not routinely indicated[21-25] except in the occasional case of rapidly progressing advanced disease or if adjuvant therapy is started in the first trimester, which will be discussed below. The patient and her family should have the opportunity to discuss fully the implications of her disease, its prognosis and treatment, preferably with a trained counsellor, before coming to a decision. In the words of Byrd 'in the face of general enthusiasm for terminating the pregnancy, we believe the evidence is that the cancer should be terminated.'

As most tumours are hormone-insensitive, it would seem that routine abortion is futile[13]. Clark found that therapeutic abortion actually decreased length of survival[14]. Milk production, however, should be suppressed (by bromocriptine) to reduce the size and vascularity of the breasts preoperatively and to lessen the risk of infection and milk fistulae.

Surgical resection of breast tumours is usually the first line of treatment in both pregnant and non-pregnant patients. Anaesthesia for this poses a slightly enhanced risk in the pregnant patient due to increased blood volume and coagulability, positional fall in blood pressure, decreased lung capacity and slow gastric emptying. American authors often recommend radical surgery in the hope that this will avoid the need for adjuvant treatment. However in the light of current knowledge about the biology of this disease, it would appear that local control can usually be adequately achieved with conservative surgery with or without radiotherapy, and the need for chemotherapy and hormone therapy will depend on other staging procedures including lymph node status and the biology of the tumour. The value of adjuvant treatment in these cases is now established[26].

The use of tamoxifen in pregnancy is largely undocumented and its safety has been questioned although there is no evidence for any teratogenic effects[27]. Goserelin (Zoladex) is also now being used to treat premenopausal women with breast cancer. Its effects on the fetus when used during pregnancy are unascertained. However it has been used successfully by gynaecologists for hypothalamic infertility and to shrink leiomyomas of the uterus prior to myomectomy to enable fertility to be preserved. Ovarian ablation, surgical or radiological, has no place in the treatment of these women[14].

The risks to the fetus from irradiation of the afflicted breast will very much depend upon the dose of radiation, distance of fetus from the field (hence gestational age), field size and energy of the radiation. These factors are calculable. Additionally, the teratogenic effects will depend upon gestational age - pre-implantation there is usually an 'all-or-nothing' fetal response - the fetus either aborting or surviving normally; in the first trimester organogenesis may be affected; excessive dosage in the second trimester may very occasionally cause microcephaly and there

is a theoretical risk of increased childhood cancers at all ages. Evidence for this largely dates from the atomic bombs dropped on Japan in 1945. The Japanese data showed an air dose of 30 cGy caused 30% of fetuses between 6 and 11 weeks gestation to be brain damaged, whilst as little as 10 cGy caused 11% brain abnormalities (compared to 4% in non-irradiated controls). It may be argued that there is no permissible dose to the fetus, but pragmatically a dose of <5 cGy is probably reasonably safe. Most of the radiation a fetus will receive during radiotherapy to the mother will be from internal scatter - in a 12 week shielded fetus this will amount to up to 30 cGy with a standard 5000 cGy course[28]. A larger fetus may receive a higher dose of radiation although the teratogenic effects are likely to be less. This is in contrast to a dose of only 0.008 cGy from a chest X-ray or 0.04 cGy from a pelvic X-ray to the patient - and considerably less to the fetus. Consequently it is clear that radiotherapy should be avoided if at all possible in the first trimester.

The use of cytotoxic chemotherapy in pregnancy presents a theoretical danger of damage to the fetus, but actual data is sparse. McKeen in 1979[29] looked at pregnant patients with Hodgkin's lymphoma undergoing chemotherapy and reported an increase of malformations in the children born to these women; and others have documented low birth weights[10]. Other workers do not concur. Blatt in 1980[30] looked at pregnancy outcome following cancer chemotherapy in 30 pregnancies (23 patients) four of whom were pregnant during treatment, and the other 26 pregnancies occurring a median of 4 years after the conclusion of treatment. No obvious fetal abnormalities were found in the 50% aborted or the 50% delivered. Sutton in 1988[31] had similar findings - in 217 women under the age of 35 with breast cancer undergoing chemotherapy, there were 25 patients with 33 pregnancies of whom 10 had terminations, 2 spontaneous abortions, 19 normal deliveries and 2 were still pregnant. There were no abnormalities found and no adverse effect on patient survival. The long term effects of chemotherapy in terms of carcinogenesis in the offspring are unknown.

The adverse effects of chemotherapy on the fetus are undoubtably related to dose of the drug, synergism with other drugs and radiotherapy, and the pharmacology of the individual drug - aminopterin is well recognized as an abortifacient and teratogen, as are the anti-metabolites such as methotrexate, and alkylating agents.

Thus in view of the paucity of data available, the use of cytotoxics in the first trimester should be avoided if at all possible, and the risks discussed with the patient.

Fertility after treatment

The fertility of these patients after treatment depends upon what treatment they received. Tamoxifen commonly causes amenorrhoea, as does goserelin (Zoladex). Chemotherapy also frequently induces menopause, although in Sutton's series 12% of premenopausal women treated with chemotherapy subsequently became pregnant[31].

In a recent study of chemotherapy (CMF) by Richards[32] only 37% of premenopausal women under 40 years (although 97% of premenopausal women over 40 years) became amenorrhoeic. Chemotherapeutic agents most likely to affect fertility are the alkylating agents. These drugs do not appear to cause an increase in fetal abnormalities or an increase in abortion rate in subsequent pregnancies. Radiotherapy to the breast alone rarely affects fertility.

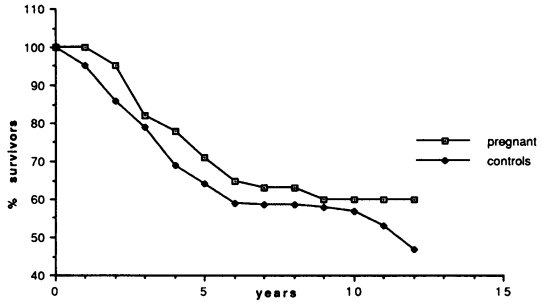

Figure 2. Survival of subsequent pregnancy group compared with that of matched controls

Subsequent pregnancies

Seven per cent of women who are fertile post-mastectomy have children[33]. There is good evidence to show that patients who go on to become pregnant after treatment for breast cancer have a better survival[14] this is partly because they are a self-selected group of those surviving long enough to become pregnant, but Peters found that even age and stage matched groups demonstrated this phenomenon[6]. Ribeiro also found that women who have subsequent pregnancies do better although this was not a statistically significant difference (see Figure 2). Thus subsequent pregnancy may protect against recurrence.

In advising a woman who has suffered from breast cancer about succeeding pregnancies, both the biological factors should be considered as well as the social, psychological and economic implications of bearing children with a potentially limited lifespan. It is for this reason that most authorities recommend a 2-3 year wait after the conclusion of treatment, so those with a poor prognosis, in whom disease is progressive or recurrent, can be identified. However couples who have been adequately counselled may yet choose to have another baby even if the woman is at high risk of recurrence and the husband is willing to undertake the role of a 'single parent', where the children may be a constant and tangible reminder of his wife.

Prognosis

Most series report that actual survival and disease-free survival are the same in gestational and non-gestational breast cancer[4,6,14,21], although a few authors[34] have found gestational breast cancer to have a worse prognosis. Nugent found that age was a more important determining factor in survival, being inversely proportional, whether the patient was pregnant or not. The preponderance of ER negativity in this group may account for this difference. Clark, however found that survival was worse in the over 40s[14], whilst Ribeiro found no association with age[21]. Others have hypothesized that prognosis is associated with the trimester of pregnancy in which the cancer is diagnosed - the first half having the better outlook[6]. This could, however, be due to a delay in diagnosis, there being more advanced disease at presentation in those diagnosed in later pregnancy.

Figure 3 summarizes the data from a number of the larger studies on survival of patients with concurrent breast cancer and pregnancy.

In conclusion it is difficult to compare many of the studies of gestational breast cancer as the patients

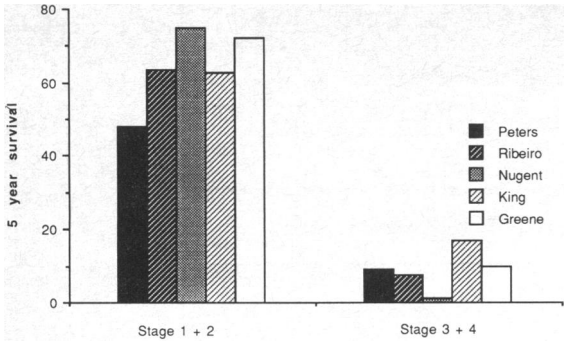

Figure 3. Concurrent breast cancer and pregnancy

included in the studies are of a heterogeneous group - some include only pregnant patients, others pregnant and lactating patients and others also include those who are subsequently pregnant. Staging systems also vary and most studies, by necessity of numbers, span many years during which treatment strategies have changed. Other studies are biased by not including non-operable patients, and of course criteria for operability vary. Nonetheless, a number of useful conclusions can be reached to offer patients with this unfortunate combination of events the most appropriate treatment:

- Does pregnancy stimulate the growth of breast cancer? On current evidence **No** - tumours neither appear more frequently nor are more aggressive in the pregnant patient.
- Should the pregnancy be terminated? **No**, unless there is a risk of teratogenesis from chemotherapy or radiotherapy in the first trimester, or unless the patient with advanced aggressive disease feels she is unable to continue the pregnancy.
- Should treatment be altered or delayed in pregnancy? **No**. The same criteria should be applied to treatment as in non-pregnant patients. The only difference may be a brief delay in the start of adjuvant therapy until after the first trimester in women who wish to keep their pregnancy, or until after delivery in those diagnosed close to term.
- Should a patient who has had breast cancer become pregnant again? **Yes**, if she wishes to. This is usually delayed at least 2 years, but may actually improve her prognosis.
- Will treatment affect the patients fertility? **Yes**, in some cases but we are unable to predict which.

Above all, the management of breast cancer in pregnancy should involve a multi-disciplinary team including a surgeon, obstetrician, general practitioner, breast counsellor and oncologist/radiotherapist if appropriate.

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